

# Does coronary CT angiography improve risk stratification over coronary calcium scoring in symptomatic patients with suspected coronary artery disease? Results from the prospective multicenter international CONFIRM registry

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## Aims

The prognostic value of coronary artery calcium (CAC) scoring is well established and has been suggested for use to exclude significant coronary artery disease (CAD) for symptomatic individuals with CAD. Contrast-enhanced coronary computed tomographic angiography (CCTA) is an alternative modality that enables direct visualization of coronary stenosis severity, extent, and distribution. Whether CCTA findings of CAD add an incremental prognostic value over CAC in symptomatic individuals has not been extensively studied.

## Methods and results

We prospectively identified symptomatic patients with suspected but without known CAD who underwent both CAC and CCTA. Symptoms were defined by the presence of chest pain or dyspnoea, and pre-test likelihood of obstructive CAD was assessed by the method of Diamond and Forrester (D–F). CAC was measured by the method of Agatston. CCTAs were graded for obstructive CAD (>70% stenosis); and CAD plaque burden, distribution, and location. Plaque burden was determined by a segment stenosis score (SSS), which reflects the number of coronary segments with plaque, weighted for stenosis severity. Plaque distribution was established by a segment-involvement score (SIS), which reflects the number of segments with plaque irrespective of stenosis severity. Finally, a modified Duke prognostic index—accounting for stenosis severity, plaque distribution, and plaque location—was calculated. Nested Cox proportional hazard models for a composite endpoint of all-cause mortality and non-fatal myocardial infarction (D/MI) were employed to assess the incremental prognostic value of CCTA over CAC. A total of 8627 symptomatic patients

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(50% men, age  $56 \pm 12$  years) followed for 25 months (interquartile range 17–40 months) comprised the study cohort. By CAC, 4860 (56%) and 713 (8.3%) patients had no evident calcium or a score of  $>400$ , respectively. By CCTA, 4294 (49.8%) and 749 (8.7%) had normal coronary arteries or obstructive CAD, respectively. At follow-up, 150 patients experienced D/MI. CAC improved discrimination beyond D–F and clinical variables (area under the receiver-operator characteristic curve 0.781 vs. 0.788,  $P = 0.004$ ). When added sequentially to D–F, clinical variables, and CAC, all CCTA measures of CAD improved discrimination of patients at risk for D/MI: obstructive CAD (0.82,  $P < 0.001$ ), SSS (0.81,  $P < 0.001$ ), SIS (0.81,  $P = 0.003$ ), and Duke CAD prognostic index (0.82,  $P < 0.0001$ ).

## Conclusion

In symptomatic patients with suspected CAD, CCTA adds incremental discriminatory power over CAC for discrimination of individuals at risk of death or MI.

## Keywords

coronary CT angiography • coronary artery calcium • coronary artery disease • symptomatic • prognosis

## Introduction

Coronary artery calcium (CAC) scoring has been validated as a robust method to effectively stratify the risk of future adverse cardiovascular events in asymptomatic patients in a manner incremental to traditional clinical risk scoring and risk factors.<sup>1–3</sup> An absent or low coronary artery calcium is associated with a low risk of future cardiac events in asymptomatic patients.

Recently, coronary computed tomographic angiography (CCTA) has emerged as an accurate non-invasive method for the evaluation of coronary artery disease (CAD) stenosis severity, extent, and distribution<sup>4–6</sup> and has been shown to have a prognostic value in a wide variety of patient settings.<sup>7</sup> When examined in asymptomatic patients, CCTA has not shown an incremental prognostic value over CAC.<sup>8–10</sup> In symptomatic patients, however, the incremental prognostic utility of CCTA over CAC has not, to date, been extensively examined. In a large international multisite cohort of symptomatic individuals with suspected but without known CAD undergoing both CAC and CCTA, we evaluated the prognostic utility of CCTA findings of CAD over CAC.

## Methods

### Design

The rationale and design of CONFIRM (CORonary CT Angiography EvaluationN For Clinical Outcomes: an InteRnational Multicenter Registry) has been previously described.<sup>11</sup> Briefly, CONFIRM is a multicenter international, open-label, dynamic observational cohort study that prospectively collects clinical, procedural, and follow-up data on patients who underwent  $\geq 64$ -detector row CCTA between 2003 and 2009. The study herein represents consecutive symptomatic patients enrolled at 12 centres in six countries (Canada, Germany, Italy, Korea, Switzerland, and USA).

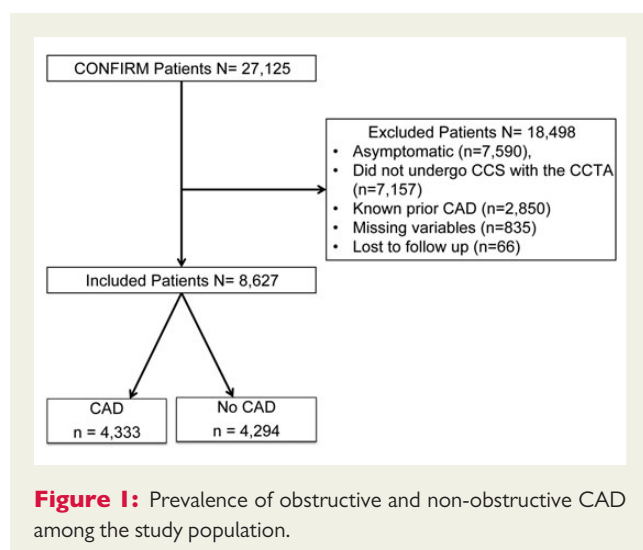
### Patients

A total of 27 125 patients comprise the CONFIRM cohort, of which 8627 met the inclusion criteria for the present study (Figure 1). Adult patients were included if they were symptomatic with suspected but without known CAD who were followed for the composite endpoint of all-cause mortality and non-fatal myocardial infarction (MI). Symptoms suspicious of CAD were defined by the presence of chest pain or dyspnoea. Patients were excluded if they were asymptomatic ( $n = 7590$ ),

did not undergo CAC with the CCTA ( $n = 7157$ ), had known prior CAD ( $n = 2850$ ), patients with missing variables (including those with poor image quality) ( $n = 835$ ), or lost to follow-up ( $n = 66$ ). Baseline characteristics and demographics as well as data necessary to calculate the Diamond–Forrester score (D–F)<sup>12</sup> were obtained by direct interview of the patients at each site by a physician or nurse coordinator, with D–F was calculated for every patient. The study protocol was approved by the Institutional Review Boards and/or Ethics Committees of each site.

### Data acquisition and image analysis

Image data were acquired by CT scanners of  $\geq 64$ -detector rows. Patient preparation, acquisition, and interpretation of CCTA and CAC data as well as clinical results were performed in accordance with the Society of Cardiovascular Computed Tomography guidelines by board certified cardiovascular CT and/or level III equivalent experts.<sup>13</sup> CAC scores were measured based on the scoring system described by Agatston et al.<sup>14</sup> CAC were categorized into four groups; as 0, 1–99, 100–399, and  $\geq 400$ . CCTAs were interpreted on a per-patient, per-vessel, and per-segment basis, with a 15-segment coronary artery tree model employed [left main; proximal, mid, and distal left anterior descending (LAD) artery; first and second diagonal branches of the LAD artery; proximal and distal left circumflex (LCx) artery; first and second obtuse marginal branches of the LCx artery; proximal, mid, and distal right coronary artery; posterior descending artery; and posterolateral branch (left or right)]. In addition, coronary artery plaque scores were calculated for overall plaque burden by the extent and severity of CAD using a segment stenosis score (SSS) and segment-involvement score (SIS). SSS was used as a measure of coronary plaque burden. Each individual segment was scored from 0 to 3 (normal to severe) luminal obstruction. After this, scores of all 15 individual segments were summed to give a total score ranging from 0 to 45. CAD was defined as the presence of any coronary plaque. As a measure of CAD distribution, the SIS was calculated based on just the presence of plaque within a segment, irrespective of the degree of luminal stenosis within each segment (minimum = 0; maximum = 15).<sup>15</sup> Further, a modified Duke CAD index—combining the location, extent, and severity of coronary stenoses—was determined in a manner that provides incremental and linear gradations of prognostic risk of incident death in relations to the extent and severity of CAD.<sup>15,16</sup> Within the Duke CAD index, eight groups were considered: Group 0 = no CAD; Group 1 =  $\geq 1$  segment with 1–49% stenosis; Group 2 =  $\geq 2$  segments with 1–49% stenosis and at  $\geq 1$  proximal segment with any stenosis; Group 3 =  $\geq 1$  segment with 50–69% stenosis; Group 4 =  $\geq 2$  segments with 50–69% stenosis or  $\geq 1$  segment with  $\geq 70\%$  stenosis; Group 5 =  $\geq 3$  segments with 50–69% stenosis or  $\geq 2$  segments with  $\geq 70\%$



stenosis or pLAD with  $\geq 70\%$  stenosis; Group 6 =  $\geq 3$  segments with  $\geq 70\%$  stenosis or  $\geq 2$  segments with  $\geq 70\%$  stenosis and pLAD with  $\geq 70\%$  stenosis; Group 7 = left main with  $\geq 50\%$  stenosis. Based on these gradations and their associated prognosis, patients were also categorized into two separate groups that included non-high-risk CAD (Groups 0–4) and high-risk CAD (Groups 5–7).

In each coronary artery, coronary atherosclerosis was defined as any tissue structures of  $>1\text{ mm}^2$  that existed either within the coronary artery lumen or adjacent to the coronary artery lumen that could be discriminated from surrounding pericardial tissue, epicardial fat, or the vessel lumen itself. Coronary atherosclerotic lesions were quantified for stenosis by visual estimation. Coronary artery plaque was quantified on both per-patient assessment: visual estimation of the stenosis into four categories; none (0% stenosis), mild (1–49% stenosis), moderate (50–69% stenosis), and severe ( $\geq 70\%$  stenosis). CAD was defined as the presence of any plaque. Obstructive CAD was defined as  $\geq 50\%$  luminal stenosis.

### Patient follow-up and events

The primary endpoint was a composite of death or non-fatal MI, with follow-up occurring for a median duration of 25 months (interquartile range 17–40 months). Data required for death was obtained by the national death index in US sites while direct interview, telephonic encounter, or review of medical records was performed within non-US sites. MI was defined as per the universal definition of MI.<sup>17</sup> Ascertainment of MI was obtained by direct interview, telephone calls, and/or medical record review at all sites.

## Statistical analysis

Continuous variables are expressed as means  $\pm$  standard deviation, whereas categorical variables are presented as absolute values and percentages. Group comparisons were carried using the  $\chi^2$  test or Fisher's exact test for categorical variables and Student's *t*-test for continuous variables. Kaplan–Meier analysis was used for survival analysis, and the different CAC and CCTA groups were compared with the log–rank test. Multiple nested Cox proportional hazard models were used to determine the incremental prognostic value of CCTA over CAC, and pre-test likelihood as determined by D–F

analysis. The predicted risk was calculated for each model, and the area under the curve (C-index) was calculated for each model in order to discriminate individuals at risk of the composite endpoint. We further performed secondary analyses restricted to patients with any evidence of atherosclerosis by CAC, as well as those with CAC of  $>10$  Agatston units. The latter of these was chosen for a clinically meaningful cut-off with a sufficient number of clinical events ( $n = 115$ ) to provide adequate statistical power ( $\beta > 0.80$ ). The *P*-value under 0.05 was considered statistically significant, and all analyses were performed with STATA version 11.

## Results

### Study cohort

The characteristics of the patients in the study cohort are summarized in Table 1. Atypical chest pain was the most frequently reported symptom (66.1%). Of the study population, 25, 65, and 10% of the patient population were considered the low, intermediate, and high pre-test likelihood of CAD by D–F classification. Patients with obstructive or non-obstructive CAD were older and more often male, with a higher prevalence of hypertension, diabetes, current smoking, and dyslipidaemia (Table 1).

### Coronary artery calcium

Coronary calcification was detected in 3766 (43.7%) patients. Among patients with detectable calcium, the mean CAC was  $260 \pm 485$  and the median CAC was 78 (25–75th, interquartile range 16–286). A total of 730 (8.5%), 1333 (15.5%), 990 (11.1%), and 713 (8.3%) patients had CAC of 1–9, 10–99, 100–399, and  $\geq 400$ , respectively.

### CAD by CCTA

Evidence of CAD by CCTA was present in 4294 (49.8%) patients, and obstructive CAD was present in 749 (8.7%) patients. Higher CAC was associated with a greater extent of CAD ( $P < 0.001$ ). The mean SIS and SSS were  $1.74 \pm 2.58$  and  $2.29 \pm 3.89$ , respectively. Using the Duke CAD classification, 618 (8%) patients had high-risk anatomy.

### Follow-up and outcomes

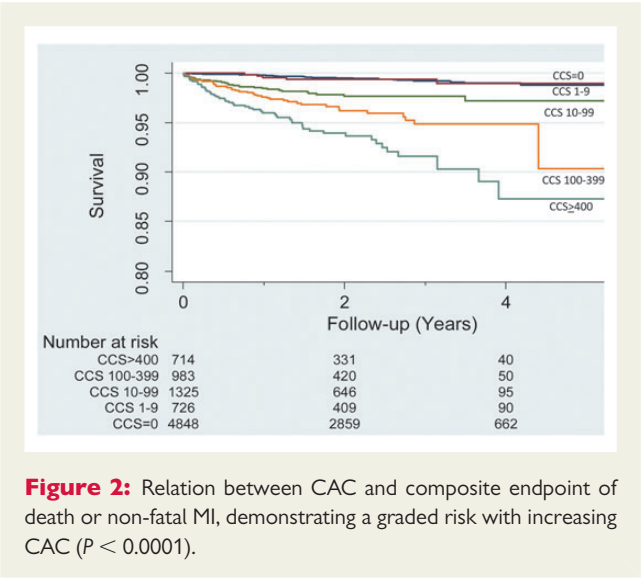
After a median follow-up of 25 months, 95 patients died and 64 experienced MI (9 fatal and 55 non-fatal). The composite outcome composed of non-fatal MI or death occurred in 150 patients. A graded increase in the risk of death or non-fatal MI existed with increasing CAC (Figure 2) and the presence of obstructive CAD by CCTA (Figure 3). Among patients with a zero calcium score, plaques were detected in 828 patients. There was a trend towards an increased event rate among patients with plaques and zero calcium score ( $P = 0.07$ ) (Figure 4). In every CAC group, there was a graded increased in the annual event rate with the presence of non-obstructive CAD and obstructive CAD on CCTA (Figure 5).

By univariate analysis, increased hazards for death or non-fatal MI were observed with increasing CAC ( $P < 0.0001$  for trend), with higher rates of events for individuals with CAC scores between 10–99, 100–399, and  $>400$  when compared with individuals with no evident calcium (Table 2). Among 4860 patients with a zero

**Table 1** Baseline characteristics

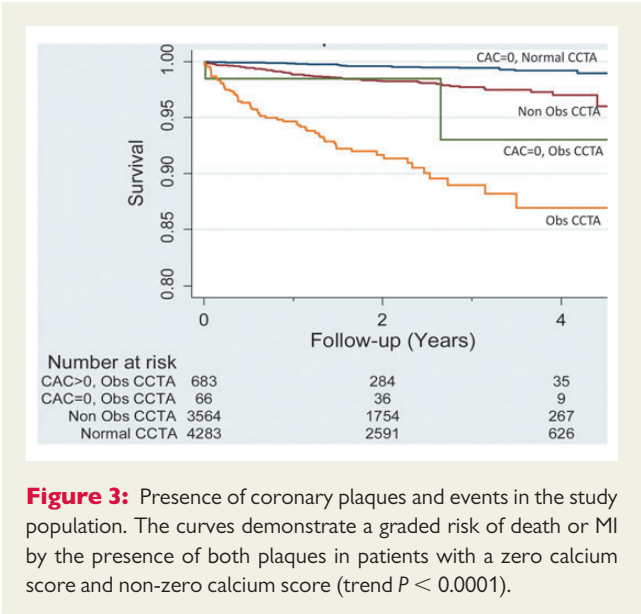
Variables	Total	Obstructive CAD >70%	Non-obstructive CAD	No CAD	Trend P-value
N	8627	749 (8.7%)	3584 (41.5%)	4294 (49.8%)	
Age (years)	56.5 ± 12	62.8 ± 10.4	60.1 ± 10.6	51.9 ± 11.6	<0.001
Gender (female %)	50%	236	1596	2483	<0.001
Diabetes mellitus, n (%)	1139 (13.2%)	168 (22%)	595 (16.6%)	376 (8.7%)	<0.001
Dyslipidaemia, n (%)	4847 (56.2%)	528 (69%)	2206 (61%)	2113 (50%)	<0.001
Hypertension, n (%)	4346 (50.4%)	516 (67%)	2038 (57%)	1792 (42%)	<0.001
Current smoking, n (%)	1464 (17.0%)	205 (24%)	600 (16%)	659 (16%)	<0.001
Family history of premature CAD, n (%)	2487 (28.8%)	321 (39%)	1055 (29%)	1111 (27%)	<0.001
Pre-test likelihood					
Low	4226 (49%)	247 (33%)	1720 (48%)	2259 (60%)	<0.001
Intermediate	3623 (42%)	337 (45%)	1578 (44%)	1708 (36%)	
High	778 (9%)	165 (22%)	286 (8%)	327 (4%)	
BMI (kg/m <sup>2</sup> )	27.5 ± 5.3	28.0 ± 5.1	28 ± 5.5	26.9 ± 5.3	<0.001
Calcium score ≥400, n (%)	714 (9%)	317 (42%)	397 (11%)	0	<0.001
Zero calcium score, n (%)	4860 (56%)	66 (9%)	764 (16%)	4030 (75%)	<0.001

CAD, coronary artery disease; BMI, body mass index.



**Figure 2:** Relation between CAC and composite endpoint of death or non-fatal MI, demonstrating a graded risk with increasing CAC ( $P < 0.0001$ ).

calcium score, only 66 (1.36%) patients had evidence of obstructive CAD and 31 events occurred in these patients (annual event rate of 0.30%), of whom 22 had normal-appearing CCTA (annual event rate of 0.24%); 9 events (21 death and 10 MI) occurred in patients with zero CAC and CAD by CCTA. On CCTA, multiple measures of CAD were associated with increased hazards for death or MI, with the presence of obstructive CAD showing with an eight-fold increase in risk of death or MI (hazards ratio [HR] 8.2, 95% confidence interval [95% CI] 5.9–11.4). Similarly, CCTA scores measuring CAD extent and distribution were associated with greater risk of adverse events by the SSS (HR 1.15 per stenosed segment, 95% CI 1.13–1.17) and SIS (HR 1.31 per-segment involved, 95% CI 1.25–1.36).

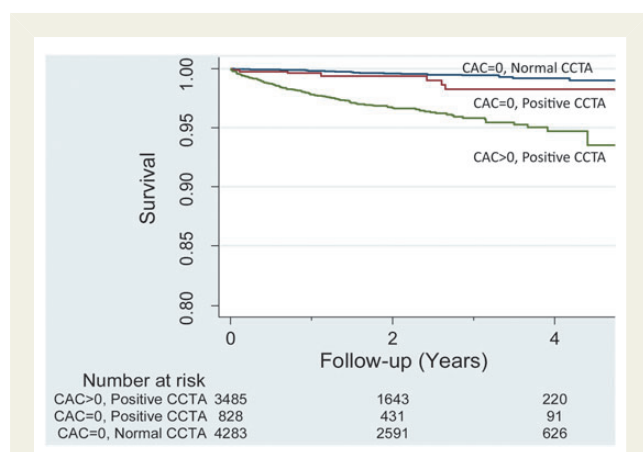


**Figure 3:** Presence of coronary plaques and events in the study population. The curves demonstrate a graded risk of death or MI by the presence of both plaques in patients with a zero calcium score and non-zero calcium score (trend  $P < 0.0001$ ).

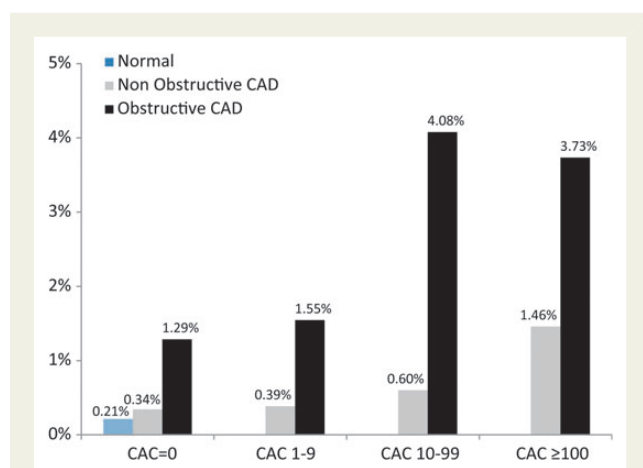
**Multivariable Cox models of CAC and CCTA**

In multivariable models accounting for clinical risk factors including age, gender, hypertension, diabetes, dyslipidaemia, and current smoking, CACS of >400 (HR 4.8; 95% CI 2.9–8.1;  $P \leq 0.0001$ ) was significantly associated with future death or MI. CCTA models were predictive of adverse outcomes by the presence, extent, and distribution of CAD ( $P < 0.05$  for all; Table 2). The presence of any obstructive CAD was independently associated with increased risk of D/MI (HR 3.9; 95% CI 2.7–5.5). In addition, measures of the





**Figure 4:** Interaction between calcium score, obstructive (obs) CAD on CCTA and events in the study population. The curves demonstrate a graded risk of death or MI by both the presence of obstructive CAD in patients with a zero calcium score and the presence of both non-obstructive and obstructive CAD (trend  $P < 0.0001$ ).



**Figure 5:** Annual event rates across the spectrum of calcium score. In every calcium score group, there was a graded increase in the annual event rate with the presence of non-obstructive and obstructive CAD on CCTA (all  $P < 0.05$ ).

extent of CAD were predictive of D/MI including the presence of left main disease (HR 1.7; 95% CI 1.2–2.4), SSS (HR 1.09; 95% CI 1.07–1.10), and SIS (HR 1.18; 95% CI 1.13–1.24).

## Incremental value of CAC and CCTA for the prediction of future death or MI

CAC and CCTA alone demonstrated improved discrimination over clinical risk factors for individuals at risk for future death or MI. Table 3 lists the C-statistics for the prediction of death or MI using multiple models of D–F, clinical variables, CAC, and CCTA findings. The addition of CAC resulted in improved discrimination compared with D–F and clinical variables alone. Obstructive CAD by CCTA

increased the C-index over models containing CAC (HR 0.779, 95% CI 0.737–0.820). Similarly, the addition of SSS or SIS also increased C-statistics compared with D–F and clinical factors alone, even when combined with CAC ( $P < 0.001$  for all). For individuals classified as intermediate-to-high risk for CAD by D–F classification ( $n = 3744$ ), CCTA also improved the C-index (from 0.765 to 0.810,  $P = 0.01$ ). When restricted to only individuals with detectable calcium by CAC, CCTA findings continued to add an incremental prognostic value (Table 3). When only patients with a calcium score of  $>10$  were included (3054 patients and 115 events), obstructive CAD by CCTA similarly added an incremental value over CAC (C-index 0.727  $\rightarrow$  0.769,  $P = 0.01$ ). However, this incremental value was reduced to a trend when only patients with a calcium score of  $>100$  were included (1600 patients and 79 events; C-index 0.749  $\rightarrow$  0.714,  $P = 0.10$ ). Among patients with CCS of  $>400$ , CCTA did not add incremental value over CCS (C-index 0.674  $\rightarrow$  0.841,  $P = 0.55$ ).

## Discussion

In this large multicenter international cohort of symptomatic patients without known CAD, the present data demonstrate that findings of extent, severity, and distribution of CAD by CCTA add an incremental discriminatory value to identify individuals at risk of death or MI over models incorporating clinical CAD risk factors, D–F pre-test likelihood of CAD and CAC.

Chest pain and dyspnoea are common presentations for symptomatic individuals with suspected CAD in the primary care office and cardiology practice. Current ACC/AHA guidelines for the management of patients with stable angina endorse the use of exercise ECG, stress echocardiography, and myocardial perfusion imaging as acceptable modalities for the evaluation of these patients, dependent on the pre-test likelihood of CAD.<sup>18</sup>

CAC and CCTA are alternative anatomic imaging modalities that have been espoused for diagnosis and prognosis of individuals with suspected CAD. However, findings regarding the use of CAC in symptomatic patients for assessing the extent and severity of CAD and prognosis have been inconsistent.<sup>19</sup> Employing electron beam CT to quantify CAC in symptomatic individuals with suspected CAD, Schmermund *et al.*<sup>20</sup> found that calcium scanning in conjunction with CAD risk factor profiles was useful to identify or exclude invasive angiographically severe disease, defined as three-vessel and/or left main CAD. In other studies, CAC correlated with ischaemic defects by functional stress testing and offered complementary information for the prediction of short- and long-term cardiac events.<sup>21,22</sup> In contrast, Gottlieb *et al.*<sup>23</sup> showed that, in symptomatic patients referred for conventional coronary angiography, the absence of coronary calcification does not exclude obstructive CAD or the need for revascularization. In a recent systematic review of the use of CAC in symptomatic patients, the presence of any CAC resulted in a high sensitivity (range 70–100%), but relatively low specificity for predicting the presence of obstructive coronary disease among symptomatic patients subsequently referred for coronary angiography. Conversely, a CAC score of 0 in low- and intermediate-risk emergency department populations with chest pain imparted a high negative predictive value (99.4%) for events over an average follow-up of 21 months.<sup>24</sup>

**Table 2** CAC and coronary CCTA predictors of death and MI

Variables	Univariate HR	Age and gender adjusted HR	Age, gender and risk factors <sup>a</sup> adjusted HR
Calcium score			
≥ 400	13 (8.2–20.6)	6.1 (3.6–6.7)	4.8 (2.9–8.1)
100–399	7.3 (4.5–11.9)	4 (2.4–6.7)	3.6 (2.1–6.0)
10–99	3.9 (2.3–6.6)	2.5 (1.5–4.3)	2.3 (1.3–3.9)
1–9	1.2 (0.5–3.1)	0.9 (0.3–2.3)	0.8 (0.3–2.3)
0	Reference	Reference	Reference
Coronary CT angiography			
Any severe stenosis	8.2 (5.9–11.4)	4.8 (3.4–6.8)	3.9 (2.7–5.5)
Obstructive left main CAD	3.6 (2.5–5.0)	1.9 (1.3–2.7)	1.7 (1.19–2.25)
Number of vessels with obstructive CAD (per vessel)	1.75 (1.29–2.37)	1.70 (1.24–2.33)	1.64 (0.94–1.13)
Segment stenosis score (per-segment involved)	1.15 (1.13–1.17)	1.11 (1.08–1.13)	1.09 (1.07–1.10)
Segment-involvement score (per-segment involved)	1.31 (1.25–1.36)	1.21 (1.16–1.27)	1.18 (1.13–1.24)

CAD, coronary artery disease; HR, hazard ratio.

<sup>a</sup>Risk factors include hypertension, diabetes, dyslipidaemia and current smoking.**Table 3** C-statistics for prediction of 25 months risk of all-cause mortality and non-fatal MI using combined models

Model	C-statistic	95% CI	P-value	
			Compared with Model II (DF + clinical)	Compared with Model III (DF + clinical + CAC)
Entire cohort				
Model I: DF	0.554	0.502–0.605	–	–
Model II: DF + clinical <sup>a</sup>	0.781	0.740–0.822	<0.001*	–
Model III: DF + clinical + CAC	0.788	0.747–0.829	0.004	–
Model IV: DF + clinical + CAC + obstructive CAD	0.817	0.777–0.856	<0.001	0.002
Model V: DF + clinical + CAC + Duke index	0.821	0.784–0.859	<0.001	<0.001
Model VI: DF + clinical + CAC + SSS	0.814	0.775–0.853	<0.001	<0.001
Model VII: DF + clinical + CAC + SIS	0.808	0.770–0.847	0.003	0.004
Patients with detectable coronary calcium				
Model I: DF	0.521	0.464–0.578	–	–
Model II: DF + clinical	0.738	0.689–0.786	<0.001*	–
Model III: DF + clinical + CAC	0.741	0.695–0.793	0.044	–
Model IV: F DF + clinical + CAC + obstructive CAD	0.786	0.741–0.830	0.002	0.007
Model V: DF + clinical + CAC + Duke index	0.789	0.747–0.832	<0.001	<0.001
Model VI: DF + clinical + CAC + SSS	0.778	0.734–0.825	<0.001	0.002
Model VII: DF + clinical + CAC + SIS	0.769	0.723–0.814	0.018	0.044

DF, Diamond Forrester score; CAC, coronary artery calcium score; CAD, coronary artery disease; SIS, segment-involvement score; SSS, segment severity score.

<sup>a</sup>Clinical model includes age, gender, hypertension, diabetes, dyslipidaemia, and current smoking.

\*P-value compared with DF alone.

To date, evidence regarding the utility of CCTA beyond CAC in symptomatic individuals with suspected CAD is limited. In this patient population, CCTA has an excellent diagnostic accuracy to rule out or confirm CAD.<sup>5</sup> In addition, it can detect obstructive CAD even in patients with a zero or low calcium score.<sup>19</sup> Our study findings provide a clear signal that, in this symptomatic

individuals, CCTA adds an incremental value over CAC for discrimination of future death of MI, particularly in patients with CAC scores not severely elevated. Multiple measures of extent, severity, and distribution of CAD by CCTA were evaluated, and each consistently offered prognostic utility beyond CAC. Importantly, in models incorporating CAD risk factors, D–F pre-test likelihood and CAC,

measures of obstructive coronary stenosis among epicardial coronary arteries were effective at discriminating future hazards of death and MI, suggesting that identification of angiographically severe CAD by CCTA is useful for defining risk. Further, employing a multitude of additional CAD measures—including extent and distribution—the incremental discriminatory value of CCTA over CAC persisted, suggesting that overall coronary plaque burden beyond calcified plaque alone are useful for prognosticating adverse outcomes, especially in patients with a calcium score of 1–100.

We observed a low adverse event rate among individuals with CAC of 0, a finding in direct accordance with other prior studies for asymptomatic and symptomatic individuals undergoing CAD evaluation. Prior studies have evaluated the rates of angiographically severe stenosis for individuals with CAC of 0—primarily in low-risk individuals presenting with acute symptoms—and have observed a non-negligible rate of obstructive stenosis between 2 and 19%.<sup>8,23,25</sup> In our cohort, only 1.36% of symptomatic patients with a zero calcium score had evidence of obstructive CAD and suggests CAC as a potentially useful ‘gatekeeper’ to further angiographic testing. CCTA has the advantage of visualizing the non-calcified plaque in these patients, an advantage over CAC. However, it remains unclear when one should proceed to CCTA in all symptomatic patients with a zero calcium score. Prior literature suggests that high pre-test likelihood or high Framingham risk score are associated with increased odds for the presence of non-calcified obstructive plaque.<sup>26</sup>

While CCTA is an excellent non-invasive tool for the identification of anatomical CAD severity, it does not discriminate whether a stenosis causes ischaemia or not. Recently, new CT-based tools are under investigation to determine whether CCTA measures of functional flow reserve or CT perfusion may be able to differentiate between lesions that are associated with ischaemia or not. In our analysis, the ischaemic burden associated with CCTA lesions was not accounted for in our models due to the lack of functional data in our registry.

Our analysis is in agreement in prior single-centre studies that addressed the same question in a smaller cohorts.<sup>27,28</sup> In a single-centre study, Hou and colleagues followed 5007 outpatients with suspected CAD for a median period of 1081 days. At the end of the follow-up period, 363 (8.2%) patients experienced major adverse cardiac events. In multivariate analysis, the area under the receiver-operating characteristic curves increased from 0.71 for clinical risk factors to 0.82 by adding CAC and further improved to 0.93 by adding CCTA. However, the present study findings are in apparent discordance with a previous report by our group that observed no added prognostic benefit of CCTA over CAC in asymptomatic individuals.<sup>10</sup> Yet the population studied differs greatly from the prior investigation in that the present study restricted analysis of the prognostic utility of CCTA findings solely to symptomatic stable individuals only. In this cohort, we noted that the extent, severity, and distribution of CAD added an incremental value of CAC alone.<sup>29</sup> This was mostly seen primarily among patients with a calcium score of <100 and suggests that the utility of CCTA may be greatest in those with ‘moderate’ CAC scores. This finding is not unanticipated, given the remarkably poor prognosis associated with higher CAC scores (e.g. >400). We also noted that the event rate is high in the

presence of extensive coronary atherosclerosis when determined by either CAC scanning or CTA.

## Study strengths and limitations

Our study has the advantage of being multicenter and international in design—features which increase the generalizability of the present findings. Nevertheless, although prospective in nature, these observational data are not immune to the limitations of any observational registry, including referral and selection bias. The follow-up duration was short (median 25 months). We purposely employed a composite outcome of all-cause mortality and non-fatal MIs, given the ‘hard’ end-point nature of both of these conditions. However, we did not have cause specific death in our registry. Finally, we did not evaluate the incremental value of CCTA in models that incorporate CAC and functional stress testing findings, the latter of which is recommended for use for symptomatic individuals with suspected CAD, but was lacking in the present study.

## Conclusion

Incremental to D–F pre-test likelihood, CAD risk factors, and CAC, CCTA improves discrimination of symptomatic individuals at risk of death or MI.

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